REMARKS

In the interest of compact prosecution, Applicants hereby amend independent claim 1 to incorporate features found in dependent claim 2 and accordingly cancels claim 2. As such, claims 1, 3-5, and 8-18 are all the claims pending in the application.

Present Claims Define Allowable Subject Matter

Claims 1-5, 8-18 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hahn et al. (US Patent No. 5,804, 203, "Hahn et al.") in view of De Lacharriere et al. (US Patent No 5,866,168, "De Lacharriere"), Denhem et al. (Radiotherapy & Oncology, 2002, 63, 129-145, "Denhem"), Remington's Pharmaceutical Sciences (17th ed. 1985 page 1121-1122, "Remington's"), Hahn (Dermatol. Surg., 1999, 25, 689-694, "Hahn"), Decaris et al. (Arthritis & Rheumatism, 1999, 42, 9, 1951-1960; "Decaris"), and Lambert et al. (Clin. Exp. Immunol., 1998, 113, 269-275, "Lambert").

Applicants respectfully disagree and traverse the rejection for the following reasons.

First, the combination of the cited references fails to teach or suggest a treatment of a sub-dermal inflammation in any soft tissue by administering a strontium compound.

Specifically, Hahn et al. does not teach or suggest any treatment of a sub-dermal inflammation in a soft tissue because Hahn et al. does not even disclose any treatment of an inflammation or any inflammation in sub-dermal level. As discussed in the previous Amendment filed on February 6, 2009, Hahn et al. is concerned with the use of strontium in methods for reducing mere skin irritation and is solely concerned with diseases and conditions associated with the surface of the skin. *See* Pages 6-7, *Amendment filed on February 6, 2009.*

In making the rejection, the Office maintains that Hahn et al. discloses "that strontium is effective in suppressing skin irritation due to ... tissue inflammation ... (Column 9, lines 13-25)." Page 2, *Office Action of May 12, 2009.* However, as discussed in the previous Amendment filed on February 6, 2009, the Examiner's cited passage opens with the language "Accordingly, it is desirable to identify agents which are effective in the skin..." (emphasis added). Use of the language "in the skin" implies that such agents will be effective in the dermal or upper layers of the skin. This passage goes on to suggest that the strontium cation and certain aqueous-soluble salts thereof are "effective in suppressing skin irritation due to sources such as chemical and environmental exposure, or tissue inflammation, injury or skin pathology." The "skin irritation" is that which is associated with the surface of the skin. The "tissue inflammation" which is mentioned is one of the potential sources of skin irritation and it is this irritation which is intended to be treated using the strontium cation. Accordingly, this passage in Hahn et al. neither suggests nor renders it obvious that the strontium cation may be effective in treating inflammation on the surface of the skin or at the sub-dermal level.

Moreover, while admitting that Hahn et al. does not expressly disclose the treatment of an inflammation with strontium, the Office states, "the prior art amply suggests the same as Hahn et al. discloses that strontium is effective in treating irritation where one of the causes of irritation includes tissue inflammation." Page 3, *Office Action of May 12, 2009.* Applicants respectfully disagree. Specifically, in treating any given symptom of a condition, such as the irritation, it does not follow that any active agent would necessarily have an effect on the underlying cause of that symptom, such as the tissue inflammation.

Accordingly, Applicants submit that Hahn et al. does not teach or suggest any treatment of a sub-dermal inflammation in a soft tissue.

The Examiner asserts, "there is no requirement that Hahn et al. specifically disclose that strontium is effective treatment of inflammation per se. However, Hahn et al. in view of Hahn does suggest that strontium also functions as an anti-inflammatory." Page 6, *Office Action of May 12, 2009.* However, Applicants respectfully note that present claims recite "inflammation [that] is sub-dermal," not just any inflammation. Accordingly, Hahn does not cure the deficiency of Hahn et al. because Hahn does not discloses any inflammation at the sub-dermal level as recited in the present claims.

Specifically, Hahn discloses new classes of compounds having anti-irritant properties. Topical application of strontium is found to suppress sensory irritation caused by irritant chemicals and irritant dermatitis. To the extent that Hahn makes any reference to inflammation, this is primarily in the context of inflammation which is triggered by chemical irritants and which is thus on the skin's surface. Hahn suggests that neurogenic inflammation may be important in inflammatory conditions, but does not go as far as to suggest that strontium may be used to treat any such condition, especially those at the sub-dermal level. Thus, Applicants submit that Hahn does not cure the deficiency of Hahn et al.

Further, neither Denham nor Remington cure the deficiency of Hahn et al. and Hahn in that neither of these documents proposes treating subdermal soft tissue inflammation by administering a strontium compound.

The rest of the cited references, De Lacharriere, Decaris or Lambert do not cure the deficiency of Hahn et al., Hahn, Denham and Remington.

With respect to De Lacharriere, the Examiner contends that De Lacharriere "discloses that strontium is a substance P antagonist and is effective in the treatment of... inflammatory diseases, such as rheumatoid arthritis...(Column 1)." Applicants respectfully disagree. De Lacharriere fails to teach or suggest a treatment of a sub-dermal inflammation in any soft tissue by administering a strontium compound because De Lacharriere's strontium is administered only for treating a pain associated with certain skin disorders, not inflammation.

In column 1, De Lacharriere suggests that substance P is involved in a wide range of diseases and conditions including inflammatory diseases, such as rheumatoid arthritis. Also mentioned are skin disorders such as psoriasis and acne rosacea. However, Applicants note that there is no teaching in De Lacharriere that strontium is the substance P antagonist of choice for treating any inflammatory condition. At column 1, lines 65-67, there is a generic statement that the "administration of a substance P antagonist is one of the therapeutic alternatives which are effective in all of the conditions and afflictions indicated above." However, this statement is made in the context of the prior art, and it cannot be taken to include strontium or any of the other metal salts which are the subject of the De Lacharriere since, according to the inventors, these were not known to exhibit substance P antagonizing activity prior to the invention. *See* Column 2, lines 17-21. Rather, what would be understood by the skilled reader is that the inventors went on to discover that certain metal salts (including strontium) exhibited a substance P antagonizing activity and, as such, "could be useful for treating the pain associated with the various skin conditions and/or disorders indicated above" (emphasis added). Indeed, the essence of the '168 patent is that the various metal salts which are disclosed exhibit substance P antagonizing activity and can thus be used for the treatment of and/or alleviation of pain, more

specifically pain associated with certain skin disorders, namely "zona, postzoster, scald or burns, demodicidosis, skin ulcer, fibrosis and/or controlling hypertrophic cicatrization and/or treating acne rosacea." Column 2, lines 33-41.

Given the wide range of conditions and disorders involving substance P which are listed in Column 1 of De Lacharriere, it would not necessarily follow that all, or indeed any, of the newly discovered substance P antagonists described in this document would be suitable for treating these conditions, let alone the substance P antagonists (strontium salts). It is only with the benefit of hindsight knowledge of the applicant's invention that the Examiner is able to select strontium salts as the substance P antagonists for use in combating "inflammatory diseases."

Moreover, neither Denham nor Remington cure the deficiency of the rest of the cited references. Decaris and Lambert are concerned with substance P and its potential involvement in inflammatory mechanisms. However, whilst substance P is known to play a role in the inflammatory process, this is just one of several mediators which are involved, and not all known substance P inhibitors have the effect on inflammation.

Substance P was considered a central mediator required for fuelling the inflammatory processes and in the transmission of pain. On this basis, a number of substance P antagonists were synthesised by the pharmaceutical industry. However, despite several clinical trials, none of these has shown any effect in patients suffering such indications. This strongly indicates that substance P is not involved in these processes, or alternatively that substance P is not rate-limiting in these processes, and therefore that a substance P antagonist will not necessarily have the desired therapeutic effect in humans.

Even having regard to the teaching in De Lacharriere that strontium salts may exhibit substance P antagonizing activity, it would thus not necessarily follow that these may be effective in combating inflammation, especially due to the involvement of other mediators in the inflammatory process. Furthermore, having regard to the points made above relating to the perceived difficulties in obtaining a sufficiently high concentration of strontium at the sub-dermal level such that this may effectively compete with calcium, strontium would not be the candidate of choice from amongst those listed in De Lacharriere.

For the reasons set forth above, Applicants respectfully submit that the combination of the cited references fails to teach or suggest a treatment of a sub-dermal inflammation in any soft tissue by administering a strontium compound.

Second, from reading the cited references, one of ordinary skill in the art would have no reasonable expectation of success to combat a sub-dermal inflammation in soft tissue by administering a strontium compound on the surface of skin as recited in the present claims. As M.P.E.P. § 2143.02 states, "[r]easonable [e]xpectation of [s]uccess [i]s [r]equired. ... [o]bviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991); *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Specifically, as discussed in the previous Amendment filed on February 6, 2009, strontium is chemically very similar to calcium and it is therefore most likely that it asserts its

anti-inflammatory properties as a calcium antagonist, inhibiting certain calcium-regulated processes. On the skin's surface and *in vitro* where the concentration of calcium is naturally low, or can be kept low, the antagonistic effect of strontium (with similar affinity to target molecules as that of calcium) can be accomplished by administering high doses of strontium so that the ratio of strontium to calcium is high. This ensures that it is the strontium which inhibits the binding of the agonist to a particular target molecule. However, sub-dermally the calcium concentration is high and it is therefore surprising that it is possible to obtain a sufficient sub-dermal concentration of strontium for this weak antagonist to exert its antagonistic effect on calcium-mediated processes, especially in cases (e.g. administration to humans) where transdermal permeability is very low.

The sub-dermal, soft tissue and blood concentration of calcium is very stable and any increase or decrease in calcium concentration is associated with significant adverse effects. As strontium is very similar in chemical properties to that of calcium (and can therefore replace calcium in most investigated biological reactions), it would be expected that a significant increase in subdermal strontium concentration would cause similar negative effects. It follows from this that, even with the knowledge that strontium may have a positive effect on biological processes taking place either on the surface of the skin or in the upper layers of the skin, one of ordinary skill in the art would not have a reasonable expectation that strontium formulations could be developed which, following topical administration in humans, allowed sufficient sub-dermal accumulation to affect certain biological processes without at the same inducing any unacceptable adverse effects. Accordingly, one of ordinary skill in the art would have no reasonable expectation of success in combating sub-dermal inflammation of the soft tissue by

applying strontium topically in light of the knowledge of those skilled in the art at the time of the invention.

For the reasons presented above, Applicants assert that one of ordinary skill in the art would have no reasonable expectation of success to reach the claimed invention.

Further, the Office states, "notwithstanding the amendment regarding sub-dermal and soft-tissue inflammation, the dependent claims are still directed to treatment of inflammation associated with acne vulgaris, psoriasis and radiation therapy, all of which are or included skin conditions." However, Applicants respectfully direct the Office's attention to page 1, lines 16-19 of the present specification. As disclosed in the present specification, while the recited conditions, acne vulgaris, psoriasis and radiation therapy, affect the surface of the skin, the same conditions also give rise to sub-dermal inflammation. *See* Page 1, lines 16-19. Thus, the dependent claims 14-16 reciting acne vulgaris, psoriasis and radiation therapy are directed to the treatment of such sub-dermal inflammation which are associated with the recited conditions.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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